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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,396	09/26/2003	Daniel V. Santi	300622010900	9173

7590 08/22/2007

TED APPLE (TOWNSEND AND TOWNSEND AND CREW)
379 LYTTON AVENUE
PALO ALTO, CA 94301

EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
08/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,396	SANTI ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,44,51 and 69-90* is/are pending in the application.

4a) Of the above claim(s) *16, 44, 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 69-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.

2. Applicant's response to the Office Action mailed August 21, 2006 on February 27, 2007 is acknowledged.

Claim Disposition

3. Claims 77-90 have been added. Claims 1-16, 44, 51 and 69-90 are pending. Claims 1-15 and 69-90 are under examination.

Withdrawn-Specification Objection

4. Previous objection to the specification is withdrawn by virtue of submission of an amendment.

Withdrawn-Sequence Compliance Objection

5. Previous objection to the sequence is withdrawn by virtue of submission of an amendment.

6. Applicant requested clarification of the record regarding the Restriction Requirement. Upon due reconsideration it was noted that the application was treated as a 371 with regard to the restriction language. The error occurred in an effort to be consistent with a PCT that has similar subject matter. The groupings remain, however for clarification the groups are set forth below with the classification, which demonstrates burden as the groups, have acquired a separate status in the art.

Restriction/Election

Group I, claim(s) 1-15, 24, 39 and 62 are drawn to a synthetic gene, vector, cell and method of making polyketide, classified in class 435, subclass 69.1.

Group II, claim(s) 16-21 are drawn to a gene library, classified in class 435, subclass 205.

Group III, claim(s) 22-23, 25-26 and 29 are drawn to a cloning vector, classified in class 435, subclass 466.

Group IV, claim(s) 27-28 are drawn to a vector, classified in class 435, subclass 320.1.

Group V, claim(s) 30-32 are drawn to a composition, classified in class 530, subclass 300.

Group VI, claim(s) 33 is drawn to a vector with a selectable marker, classified in class 435, subclass 476.

Group VII, claim(s) 34-37, 40-43 and 65-66 are drawn to a method of joining a series of DNA units using a vector pair classified in class 435, subclass 462.

Group VIII, claim(s) 38 and 67-68 are drawn to a method of joining several DNA units in a sequence classified in class 435, subclass 463.

Group IX, claim(s) 44-45 are drawn to a method of making a synthetic gene classified in class 536, subclass 23.1.

Group X, claim(s) 46-48 are drawn to a method for identifying restriction enzyme recognition sites classified in class 435, subclass 478.

Group XI, claim (s) 49-50 are drawn to a method for high throughput synthesis classified in class 435, subclass 7.1.

Group XII, claim (s) 51-58 are drawn to a method for designing a synthetic gene classified in class 435, subclass 4.

Group XIII, claim(s) 59-60 are drawn to a method for analyzing a nucleotide sequence of a synthon classified in class 435, subclass 6.

Group XIV, claim(s) 61 is drawn to a system for high throughput synthesis of synthetic genes classified in class 435, subclass 213.

Group XV, claim(s) 63-64 are drawn to an open reading frame vector classified in class 435, subclass 320.

New-Specification Objection

7. The specification is objected to because of the following informalities:

The specification is objected to because the originally filed claims recite the language "less than about 90%", however, no support was found in the instant specification for this language. It is suggested that the specification is amended to recite this phrase.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-15 and 69-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide segment (see for example claim 1), however, the claims do not set forth said "reference polypeptide" and are devoid of a structure, especially in view of the recited sequence identity. In addition, no functional limitation is recited in the claims for the recited "polypeptide segment", thus no correlation is made between function and structure. It is noted that claim 2 recites a PKS polypeptide segment, however, there is no indicia as to what said segment looks like or the reference structure. The claims also recite that the naturally occurring gene encodes a polypeptide that is 95% or 97% identical to the polypeptide segment encoded by the synthetic gene. Further, the claimed invention is directed to a coding segment of the gene that is less than 90% or 80% of the naturally occurring gene". Thus, the

claims encompass a large variable genus, not adequately described. The skilled artisan cannot envision the detailed chemical structure of the genus encompassed in the claims, thus the claimed invention lacks adequate written description.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus could include non-functional proteins or proteins with a different function than the one contemplated. Therefore, the genus of claimed polypeptides encompasses widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional. Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is,

for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 1-15 and 69-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabled for the full scope of the claims, for example, the specification does not reasonably provide enablement for any segment of any polypeptide having any structure and function encoded by the recited synthetic gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any

necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a large variable genus of polypeptide segments and nucleic acid segments encoding said polypeptide. Note that the claims are directed to a synthetic gene encoding a polypeptide segment that corresponds to a reference polypeptide, however, the claims do not set forth said "reference polypeptide" and are devoid of a structure. In addition, no functional limitation is recited in the claims for the recited "polypeptide segment" to correlate a structure with function. It is noted that claim 2 recites a PKS polypeptide segment, however, there is no indicia as to what said segment looks like or the reference structure. Further, the claimed invention is directed to a coding segment of the gene that is less than about 85% or 90% of the naturally occurring gene" (see for example claims 69, 75 and 90) or directed to a coding segment of the gene that is less than 80% of the naturally occurring gene" (see for example claim 85). Thus, the claims encompass a large variable genus, not adequately described. Due to the large quantity of experimentation necessary to generate the infinite number of fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation

would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein

having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) discloses an established database of nucleotide substitutions, deletions, insertions and rearrangements. The database demonstrates the deleterious impact that various point mutations, deletions and insertions have on the function of a Factor VIII protein. Furthermore, Tuddenham et al. demonstrates that a change of only a single nucleotide may result in loss of function in the protein product (see page 3512 of the reference). Therefore, the art speaks to the high degree of unpredictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity. The art also demonstrates that detailed knowledge of the ways in which the protein's structure relates to its function is necessary hence the need for exemplification or guidance/direction in the instant specification.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of

routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed modifications in the gene and the protein product. The nature and properties of this claim is difficult to ascertain from the examples provided, as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments for the gene and the gene product. The claims broadly read on any structure and function is not supported by the instant specification. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1-15 and 69-90 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 1, 75, 85-86, 88, 90 and the dependent claims hereto are indefinite for the recitation of "a polypeptide segment that corresponds to a reference polypeptide", as it is unclear what "reference polypeptide is being referred to because no structure is recited in the claims, especially in view of the recited percent identity. For instance, 95% identical to what structure.

Withdrawn-Claim Rejections - 35 USC § 102

11. Previous rejection to the claims under 35 U.S.C. 102 is withdrawn in favor of the objection made to the specification to allow applicant to amend the specification to include the information recited in the claims since the filing of the application which may impact claim interpretation.

Response to Applicant's Arguments:

12. Applicant's arguments have been fully considered and the rejections/objections of record have been withdrawn. Note however, that new objections and rejections have been instituted based on applicant's amendments to the claims for the reasons stated above.

Conclusion

13. No claims are allowable.

14. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

HOPE ROBINSON
PRIMARY EXAMINER

Hope Robinson, MS
Primary Examiner
8/20/07